UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,221	08/19/2003	Hitoshi Nagaoka	1217-031377	6470

28289 7590 09/02/2008

THE WEBB LAW FIRM, P.C.
700 KOPPERS BUILDING
436 SEVENTH AVENUE
PITTSBURGH, PA 15219

EXAMINER	
MARX, IRENE	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
09/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HITOSHI NAGAOKA

Appeal 2008-3448
Application 10/644,221
Technology Center 1600

Decided: September 2, 2008

Before DEMETRA MILLS, RICHARD M. LEBOVITZ, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for treating HIV using a mycelium extract which the Examiner has rejected as indefinite and failing to enable the claims. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Background

"It was reported that the first deceased [person] by HIV-infection in the world was found in Africa in 1950, and . . . HIV-infected persons spread all over the world" (Spec. 1). The Specification discloses that "therapeutic agents for the HIV-infected persons include AZT, ddI, ddC, interleukin-II, GL0223, DHCA, γ-beta-ser Interferon, alpha interferon, gamma interferon" (Spec. 1). The Specification also describes prior art which reported that the "lentinan obtained from *Lentinus edodes* inhibits proliferation of HIV by the use thereof in combination with the HIV therapeutic agent AZT" (Spec. 2).

Appellant teaches that the "HIV activity inhibitor comprising the *Lentinus edodes* mycelium extract obtained by the [Specification's] process inhibits viral activity of Hepatitis B virus and HIV, is able to restrain proliferation of said virus and is excellent in the safety by virtue of less anxiety of side effects" (Spec. 3).

Statement of the Case

The Claims

Claims 1 and 2 are on appeal. Claims 1 and 2 read as follows:

> 1. A method for treating a human infected with human immunodeficiency virus (HIV), comprising:
>
> (a) inoculating *Lentinus edodes* fungus in a solid culture medium comprising 90 parts by weight of bagasse and 10 parts by weight of rice bran to yield proliferated mycelium;
>
> (b) disentangling the solid culture medium containing the proliferated mycelium so that the amount of the bagasse of 12-in mesh is not more than 30% by weight and adding thereto 1 to 10 kg of water and 0.5 to 5 g of at least one enzyme selected from the group consisting of cellulase,

protease and glucosidase based on 1 kg of the disentangled solid culture medium, while keeping the solid culture medium at 30 to 50°C, to give a bagasse-containing mixture;

(c) grinding and milling the bagasse-containing mixture so that the amount of the bagasse of 12-in mesh is not less than 70% by weight;

(d) heating the ground and milled bagasse-containing mixture to a temperature of 75 to 95°C to inactivate the enzyme;

(e) filtering the resultant mixture through a filter cloth of 50 to 120-in mesh to thereby obtain a purified, concentrated pharmaceutical *Lentinus edodes* mycelium extract; and

(f) administering orally at least one effective dose of said purified, concentrated extract to said human, wherein said extract weakens HIV activity and inhibits HIV proliferation in said human.

2. The method according to claim 1 wherein the enzyme is cellulase.

The rejections as presented by the Examiner are as follows:

A. Claims 1 and 2 stand rejected under 35 U.S.C. § 112, second paragraph, as failing to comply with the definiteness requirement (Ans. 3).

B. Claims 1 and 2 stand rejected under 35 U.S.C. § 112, first paragraph, as being nonenabled (Ans. 3).

A. 35 U.S.C. § 112, second paragraph indefiniteness rejection

Appellant argues that to "those skilled in the art of the prior art of *Lentinus edodes* infusion, the effective dose is apparent from the present specification. The present specification gives very particular direction as to how to prepare the *Lentinus edodes* infusion" (App. Br. 5). Appellant further contends that the claimed composition "is administered in beverage

amounts, which, as a practical matter, involve a few to several ounces per administration, and such administration is described, for example at specification paragraphs 28-30" (App. Br. 5).

The Examiner responds that "Appellant has not proffered prior art disclosing or discussing the administration of particular infusions or protocols for this purpose. Thus, there is no clear definition of the record of what constitutes 'at least one effective dose' in the context of the claimed invention" (Ans. 6). The Examiner also argues that the "the issue is whether one of ordinary skill in the art can readily determine what constitutes an 'at least one effective dose' . . . i.e., frequency of administration and length of treatment" (Ans. 7).

In view of these conflicting positions, we frame the indefiniteness issue before us as follows:

Is the claimed phrase "effective dose" indefinite in the context of claim 1?

Discussion of the 35 U.S.C. § 112, second paragraph rejection

We agree with Appellant that the phrase "effective dose" is definite in the context of the instant Specification. *See Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1383 (Fed. Cir. 2003)("Our predecessor court has stated that 'effective amount' is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite"). In our opinion, the Examiner is essentially arguing the enablement rejection guised in terms of definiteness (*see* Ans. 7). When the Examiner contends that "the issue is whether one of ordinary skill in the art can readily determine what constitutes an 'at least one effective dose'" (Ans.

7), the Examiner is framing the issue in enablement terms, not definiteness terms. To establish indefiniteness, the Federal Circuit noted that "[i]f the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Exxon Research and Engineering Co. v. U.S.*, 265 F.3d 1371, 1375 (Fed. Cir. 2001). In the instant context, we conclude that the amount of an "effective dose" is reasonably construed as a discernable feature that can be determined using routine experimentation, in the absence of evidence to the contrary.

We reverse the rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph.

B. 35 U.S.C. § 112, first paragraph Enablement rejection

Claims 1 and 2 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that the Specification does not enable the claimed invention (Ans. 3).

The Examiner reasons that the ordinary artisan

> would not have a reasonable expectation of success of treating a human infected with HIV by administering orally at least one effective dose of a purified, concentrated extract of *Lentinus edodes* of unknown composition, in the absence of a clear definition of what constitutes an "effective dose" and of an indication of how often and for how long such an oral dose is to be administered in order to achieve the stated purpose of weakening HIV activity.

(Ans. 6.) The Examiner argues that the "issue is whether or not it would require undue experimentation for one of ordinary skill in the art to

determine what constitutes 'at least one effective dose' in the instant context specifically and particularly to treat HIV in the manner claimed" (Ans. 10). The Examiner further contends that the "issue of the treatment of HIV cannot readily and dismissively equated with any treatment in herbal medicine" (Ans. 10).

Appellant argues that the

> essence of the present invention is not primarily in the preparation and general administration of the *Lentinus edodes* infusion, therefore, but emphasizes the infusion's new and unexpected effectiveness against HIV, such that administration of the *Lentinus edodes* infusion has an indication-specific medicinal effect even when given according to prior art dosages and routes of administration.

(App. Br. 7.) Appellant further contends that "[w]hen Appellant submitted the MT-4 results in the specification and urged such results as supportive of the asserted enablement, Appellant identified an effectiveness correlation with their enabled effective dose. The *in vitro* results in the Sawadaishi Declaration dated June 9, 1997 give further confirmation." (App. Br. 10.)

In view of these conflicting positions, we frame the enablement issue before us as follows:

Would it have required undue experimentation to treat HIV with an "effective dose" of the *Lentinus edodes* extract?

Findings of Fact (FF)

Breadth of the Claims

1. "The claims are broadly drawn to a method of treating a human infected with HIV by orally administering at least one effective dose, without amounts and concentrations." (Ans. 3.)

Presence of Working Examples

2. The Specification discloses "a single working embodiment the treatment of MT-4 cells infected with one particular strain of HIV. The data of Table 1, for example, show only inhibition of the HIV virus in MT-4 cells and not in living organisms." (Ans. 4; *see* Spec. 8.)

Amount of Direction or Guidance Presented

3. The Specification teaches a specific method to prepare the *Lentinus edodes* extract (Spec. 3-5). The Specification teaches that the "extract of *Lentinus edodes* mycelium as obtained above can be used as its concentrate, or can be used in the form of a powder obtained by freeze-drying the extract" (Spec. 5 ¶ 0028).

4. The Examiner states that "[i]t is noted that the at least one effective dose is never defined or identified in the instant written disclosure" (Ans. 3-4).

5. The Specification discloses that maximum viability of MT-4 cells infected with HIV was obtained with a dosage of 125 µg/ml of extract, with both lower and higher dosages having less effect (*see* Spec. 8, Table I).

6. The Specification discloses that the assay procedure followed was that described in "Antiviral Research"[1] (Spec. 7 ¶ 0042) which

---

[1] This article was cited on the 3/13/2006 IDS and the full citation is Yoshio Inouye et al. *In vitro antiviral activity of polyoxomolybdates. Mechanism of inhibitory effect of PM-104* $(NH_4)_{12}H_2(Eu_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4 \cdot 13H_2O$ *on human immunodeficiency virus type 1*, 20 ANTIVIRAL RESEARCH 317-331 (1993).

reference teaches a six day incubation with the virus to proceed prior to testing (Inouye 321).

State of the Prior Art and Unpredictability of the Art

7. The Examiner cites Pauwels[2] to show that while some HIV drugs are successful "a number of important therapeutic challenges remain" (Pauwels 79).

8. However, Pauwels also teaches that the "human T lymphoblastoid cell line MT-4 . . . is one of the cell types that has been extensively used in anti-HIV drug discovery efforts" (Pauwels 81).

9. Pauwels teaches that "[i]n the course of two decades, this methodology led to the first description of a number of important new anti-HIV agents and/or classes" (Pauwels 81).

10. The Examiner cites Suzuki[3], which notes that "[i]t should be stressed, however, that the activity of an agent against HIV in vitro does not ensure that the agent will be clinically applicable in the setting of HIV-infection. Bioavailability, metabolic features, toxicities, and other factors may negate the usefulness of a given agent" (Suzuki 372).

11. The final section of Suzuki quoted by the Examiner notes "[n]evertheless, our findings described here and previous observations that

---

[2] Rudi Pauwels, *Aspects of successful drug discovery and development*, 71 Antiviral Research 77-89 (2006).
[3] Harumi Suzuki et al., *Inhibition of the infectivity and cytopathic effect of Human Immunodeficiency Virus by water-soluble lignin in an extract of the culture medium of Lentinus Edodes Mycelia (LEM)*, 160 Biochemical and Biophysical Research Communications 367-373 (1989).

EPS4 appears to have multiple biological activities including apparent immunopotentiating capability together with an activity against HIV in vitro warrant for further investigation" (Suzuki 372).

12. The Examiner states that "[a]nother issue to be considered is the degradation and loss of antiviral effects in the complex physiological environment of the human or animal body" (Ans. 5).

13. The Sawadaishi Declaration teaches that a "highly significant percentage of patients infected with hepatitis B, after daily treatment with the Lentinus edodes mycelium extract of the present invention, showed a remarkable improvement in their serum liver enzymes" (Sawadaishi Declaration 2/28/03, 3).

14. The Sawadaishi Declaration teaches that treatment using the mycelium extract showed "a complete lack of adverse side effects" (Sawadaishi Declaration 2/28/03, 3).

Quantity of Experimentation necessary and Level of Ordinary Skill

15. The Examiner made no factual findings regarding the quantity of experimentation necessary to carry out the invention or the level of ordinary skill.

Discussion of 35 U.S.C. § 112, first paragraph Enablement rejection

"The essential question here is whether the scope of enablement ... is as broad as the scope of the claim[s]." *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991). We agree with the Appellant that the Examiner has not provided sufficient evidence to show that it would have required undue experimentation to practice of the

claimed invention. In our opinion, analysis of the *Wands* factors favors Appellant. *In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988).

We specifically find that the factor of "working examples" favors Appellant since the Appellant has shown that the mycelium extract is active against HIV (FF 2) in the same in vitro assay used in the prior art to identify other anti-HIV agents (FF 8,9).

We also find that "state of the art" and "the predictability or unpredictability of the art" factors weighs in favor of Appellant, since the prior art routinely uses the same methods to identify HIV inhibitors (FF 8, 9), the prior art teaches that the mycelium extract warrants investigation (FF 11), and the Sawadaishi Declaration shows safety of the mycelium extract in patients (FF 14) as well as bioavailability and efficacy of the mycelium extract against HBV, a different type of viral infection (FF 13). While the Examiner has shown that there is some level of unpredictability (FF 7), the Examiner's issues regarding bioavailability, toxicity, and degradation in the body (FF 10, 12) are rebutted by the Sawadaishi Declaration, which shows that an "effective dose" of the mycelium compound is sufficiently bioavailable and resistant to degradation to inhibit HBV (FF 13) as well as showing that the compound is nontoxic (FF 14).

We also find that the "amount of guidance" in the Specification is more than minimal, with the Specification showing the method of preparing the compound (FF 3) as well as effective amounts in vitro using a standard assay (FF 5, 6). We recognize that the Specification does not have extensive guidance either, with no specific dosing information (FF 4).

In our opinion, the breadth of the claims is also relatively narrow, since the claims require the use of a particular extract obtained in a particular way, for treatment of a particular disease (*see* FF 1, 3).

As we balance these factors, "[t]he question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought." *In re Brana*, 51 F.3d 1560, 1564 (Fed. Cir. 1995). In *Brana*, the court determined that "[o]nly after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." *Id.* at 1566. We conclude that the Examiner has not met her burden to show that one would doubt that the mycelium compound, shown to be effective in vitro against HIV and bioavailable in vivo against HBV (FF 5, 11, 13, 14), is not useful and enabled.

We are not persuaded by the Examiner's argument that the "issues such as bioavailability, metabolic features, and toxicities as well as other factors may negate the usefulness of a given agent" (Ans. 4). While this statement is true generically, the Examiner must provide evidence that these issues are problematic in the instant case, not simply point to generic issues in drug design. *See In re Cortright*, 165 F.3d 1353, 1357 (Fed. Cir. 1999)("The PTO cannot make this type of rejection, however, unless it has reason to doubt the objective truth of the statements contained in the written description"). In the instant case, the evidence does not support this argument since the Sawadaishi Declaration demonstrates that the *Lentinus*

edodes extract is bioavailable and non toxic (FF 13, 14) and the Specification demonstrates that the compounds have some anti-HIV efficacy (FF 5).

We also do not find persuasive the Examiner's argument regarding the "challenges and difficulties of producing anti-HIV drugs that are effective" (Ans. 5) and that "[n]o protocol is identified for oral administration of the extract to treat a human infected with the human immunodeficiency virus (HIV) such that the extract weakens HIV activity. . . . A protocol of administration to MT-4 cannot be extrapolated to humans" (Ans. 11).

While we recognize that drug development is fraught with difficulties, Pauwels also teaches that the "human T lymphoblastoid cell line MT-4 . . . is one of the cell types that has been extensively used in anti-HIV drug discovery efforts" (FF 8). This is the same drug line used by Appellant to show anti-HIV efficacy of the extract (FF 5). Further, Pauwels teaches that "[i]n the course of two decades, this methodology led to the first description of a number of important new anti-HIV agents and/or classes" (FF 9). Thus, rather than representing something outside the mainstream, Appellant's approach to identification of an HIV inhibitor falls squarely within the standard modes of the prior art (FF 8, 9). The Examiner has not provided a preponderance of specific evidence to show that the *Lentinus edodes* extract, which functions in vitro against HIV and in vivo against HBV (FF 5, 8, 9, 13, 14) would be expected not to function in vivo against HIV.

We reverse the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, enablement.

CONCLUSION

In summary, we reverse the rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph and under 35 U.S.C. § 112, first paragraph, enablement.

REVERSED

cdc

THE WEBB LAW FIRM, P.C.
700 KOPPERS BUILDING
436 SEVENTH AVENUE
PITTSBURGH PA 15219